REMARKS

The Invention

The present invention is directed to a mutant antibody comprising a reactive site not present in the wild-type of said antibody and complementarity-determining regions (CDRs) that recognize a metal chelate. The reactive site is introduced into the antibody through site-directed mutation of the nucleic acid that encodes the wild type peptide sequence.

The reactive site is in a position proximate to or within the complementarity-determining regions. The reactive site is the mutation and has complementary reactivity with a reactive group on the metal chelate. Exemplary metal chelate reactive groups include carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

Status of the Claims

After entry of this amendment, claims 1-3, 10-11, 14-25, 42, 44 and 45-46 are pending in the above-referenced patent application. Claims 1-3, 10-11, 14-25 and 42-44 were substantively examined. Claim 43 is canceled. Claims 10 and 11 are deemed to be in condition for allowance. Claim 15 is objected to as being dependent on a rejected base claim.

Claims 1-3, 16-19, 24, 42 and 44 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Stickney et al. Claim 43 is rejected under 35 U.S.C. §103(a) as being allegedly obvious over the combination of Reardan et al. in view of Orlandi et al., Pastan et al. and Goodwin et al. Claims 1-3, 14, 16-25, 30-38 and 42-44 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement.

Thus, according to the instant Office Action, claims 14, 15, 20-23, 25, and 30-38 are free of the prior art.

The Amendments

New claims 45 and 46, identical to claims 1 and 42, respectively are introduced for examination on their merits. The new merely add to claims 1 and 43 the recitation that the

reactive site is "introduced by mutagenesis of a nucleic acid encoding said wild-type of said antibody." Support for this amendment is found throughout the specification as filed. *See*, for example, page 23, lines 16-18; and Examples 3 and 4. No new matter is added by this amendment.

Although the present Action is made Final, the Examiner indicated to the Applicants representative that the entry of claims reflecting this simple and clarifying addition to the subject matter of claims 1 and 42 would be favorably considered. Accordingly, the Applicants respectfully request that the Examiner enter and consider new claims 45-46.

The Rejections

Under 35 U.S.C. §112, first paragraph

Claim 44

Claim 44 is rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. The Action states that Applicants' specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; or (2) reproducible from the written description.

The Examiner states that to enable claim 44, the CHA 255 antibody must be deposited with a third party depository. Applicants respectfully disagree.

"Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation." See, 37 CFR 1.802 (b). "No deposit is required...where the materials can be obtained from publicly available material with only routine experimentation and a reliable screening test." *See*, MPEP 2404.2.

CHA 255 and the hybridoma that expresses this antibody are known and readily available to the public; and these species can be made or isolated without undue experimentation. Moreover, these materials were known and readily available to the public prior to the filing date of the instant application. At least one scientific reference and at least one unenforceable U.S. patent disclose CHA 255 and a hybridoma expressing this antibody. Both the reference and the patent disclose how to construct the hybridoma and isolate and characterize antibodies that are produced by the hybridoma.

For example, abandoned U.S. Patent No. 4,722,892 discloses that CHA 255 is an antibody that binds to the complex formed between EDTA and indium. *See*, for example, column 2, lines 52-57. The patent describes the preparation of the KLH-EDTA-Indium (III) antigen and the immunization of mice with this antigen. Preparation of the reactive EDTA derivative coupled with KLH is disclosed in Chakrabarti et al., *Anal. Biochem.* **217**: 70-75 (1994). The '892 patent also described the production of a hybridoma that produces the CHA255 antibody. The antibodies were screened by their ability to bind ^{111}In-aminobenzyl-EDTA by a solid-phase second antibody radioimmunoassay as described in Wang et al., *J. Immunol. Methods* **18**: 157 (1977). Furthermore, a reference authored by Meares et al. (*Nature* **316**: 265-268 (1985)) describes the preparation of a CHA255 antibody and an antigen recognized by this antibody.

In view of the above, CHA255 and assays for identifying and characterizing this antibody were well described in both the patent literature and the primary scientific literature. The structure and sequence of the antibody were available in public databases, and production of the gene encoding the antibody was routine in the art at the time the instant application was filed. Moreover, a hybridoma cell line expressing this antibody and all the materials necessary to assemble the hybridoma was known in the art, and readily available to those of skill without resort due undue experimentation at the time the present application was filed. The materials necessary to prepare the antibody remain known and readily available to those of skill. Accordingly, the present invention is fully enabled and described under 35 U.S.C. §112 without resort to depositing CHA255 or a hybridoma or other cell line that produces this antibody.

Claims 1-3, 14, 16-25, 30-38, 42-44 and 45-46

Claims 1-3, 14, 16-25, 30-38, 42-44 are rejected under 35 U.S.C. §112, first paragraph as allegedly being of a scope broader than that enabled by the specification. Specifically, the Examiner expresses concern that the specification fails to enable the production of antibodies of the invention, which maintain specificity for their antigen, in which the reactive site is located within the CDR. Contrary to the Examiner's conclusion, the applicants have empirically demonstrated that a reactive site can be situated in the CDR without markedly

perturbing the ability of the antibody to recognize and bind its antigen. Moreover, the applicants have described molecular modeling techniques whereby one of skill can make a judicious choice regarding where to place the mutation without markedly perturbing the selectivity of the antibody for its antigen.

As pointed out by Dr. Meares in his declaration, filed on February 26, 2004, Example 3 of the specification sets forth the preparation of two mutant antibodies of the invention in which the mutation is within the CDR (S95→C95; and N96→C96). The mutant antibodies recognize and bind to their antigen.

As stated in Professor Meares' declaration:

> [m]ore particularly, Example 3 (page 71, line 1 to page 73, line 2) describes generation of a mutant CHA255 antibody comprising a reactive site not present on the wild type CHA255 antibody using computer aided design to identify suitable placement of a mutation...a serine residue at position 95 (S95) of the light chain of CHA255 and an asparagine residue at position 96 (N96) of the light chain of CHA255 were chosen for their proximity to the acryl group of the metal chelate...[t]he serine and asparagine was also chosen...because it was identified as a residue that was not involved in the hydrophobic interactions or hydrogen bonding between CHA255 and the metal chelate. ***Each of the substituted residues is within the CDR of CHA255***. See, page 9, lines 3-12.

Thus, the specification is fully enabling for mutant antibodies in which the reactive site is within the CDR of the antibody. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 1-3, 14, 16-25, 30-38, 42-44 under 35 U.S.C. §112, first paragraph .

In view of the above, new claims 45 and 46 are also fully enabled in compliance with the standards of 35 U.S.C. §112, first paragraph.

Since the Office Action indicates that claims 14, 15, 20-23, 25, and 30-38 are free of the art, and the applicants have demonstrated that these claims are fully enabled, Applicants request a notification of the allowability of these claims.

Under 35 U.S.C. §102(b)

Over Stickney et al. ("Stickney")

Claims 1-3, 16-19, 24, 42 and 44 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Stickney. Applicants respond to the rejections with a combination of argument and amendment.

During the teleconference, it was the impression of the Applicants' representative that the Applicants and the Examiner were substantially in agreement that Stickney teaches an antibody having two distinct Fab domains that are chemically cross-linked, forming a Fab2 species. The Examiner interprets the term "mutant" to be of a breadth sufficient to encompass a Fab2 that includes a cysteine residue covalently modified with a linker. Since Applicants claim that the mutation must be a reactive site, the cysteine-bound linker of Stickney must include a reactive group. As discussed below, Stickney is silent as to the formation of a species having the structure Fab-linker-(reactive group). Moreover, as is apparent from the scheme set forth in Stickney, such a group is not produced.

In their present form, the claims require that the mutant is a "*reactive site [that] interacts with a reactive group on said metal chelate.*" Thus, the mutant reactive site must be both ***reactive*** and must be ***available*** to interact with a metal chelate. A close reading of Stickney and careful review of FIG. 1 of the reference demonstrate that the site that the Examiner identifies as a "mutant" is not present in the conjugates of Stickney and, thus, cannot be either reactive or available.

Stickney et al. discloses functionalizing the sulfhydryl moiety of a naturally occurring cysteine residue on each Fab' fragment with a linker arm. The cysteine residue of each Fab' fragment is present in the wild type peptide, Thus, the cysteine sulfhydryl moiety itself cannot be equated with the presently claimed *reactive site*, because the applicants' claimed *reactive site* cannot be present in the wild type peptide. Accordingly, the only species that is at all amenable to interpretation as a mutant is a free maleimide group at a terminus of the linker that is not bound to a cysteine, e.g., (maleimide)-linker-Fab'. Stickney neither discloses nor suggests such a species.

The Stickney et al. linker arm is a bifunctional species that has a sulfhydryl-reactive moiety (maleimide) at each terminus. The applicants respectfully submit that the reaction scheme provided by Stickney makes it apparent that a species such as (maleimide)-linker-Fab' does not exist. In the first step of the reaction scheme, Stickney shows combining both Fab' species with the linker simultaneously. According to Stickney's reaction scheme, to the extent that (maleimide)-linker-Fab' might exist in the reaction milieu, its existence would be transient as the free maleimide would immediately couple with the cysteine sulfhydryl another Fab'. Stickney is silent regarding producing or isolating (maleimide)-linker-Fab'. Thus, the reference cannot be interpreted as teaching a reactive mutant, such as that claimed by the applicants. The reaction scheme to Stickney's antibody is shown below (*see*, page 6651)

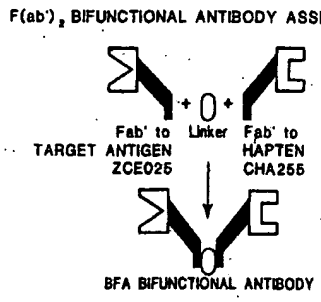


Fig. 1. Antibody fragmentation and BFA assemblage. The sulfhydryl groups of Fab' fragments of two different antibodies, one specific to CEA and one specific to a hapten carrier of radioisotope, were linked with bis-maleimidomethyl ether to form a $F(ab')_2$ BFA coupled by a stable thioether linkage.

Moreover, upon reaction with the linker arm (to form the "mutant") the chemically modified ("*mutant*") cysteines are not ***reactive***. The scheme indicates that the two Fab' species and the linker are combined to form the chimeric antibody. Thus, both maleimide moieties and both cysteine sulfhydryls are converted to a thioether. As stated in the figure legend, "***a stable thioether linkage***." Therefore, the stable thioether linkage is not a reactive site as set forth in Applicants' claims.

In view of the above, Stickney et al. cannot be interpreted as disclosing or suggesting a Fab' that includes a reactive site not found in the wild type Fab': (a) the cysteine residues are present in the wild type, thus they are not mutants; (b) the species

(maleimide)-linker-Fab' is not produced by the pathway outlined by Stickney; (c) in the dimeric Fab', the cysteine residues are neither ***reactive*** nor ***available*** to interact with a reactive group on a metal chelate, they are tied up in a stable thioether bond. In view of the above, the antibody of Stickney cannot be said to have a ***reactive*** group that interacts with a metal chelate as claimed by the applicants.

As set forth above, the disclosure of Stickney is missing at least one element of Applicants' claims. Accordingly, the rejection under 35 U.S.C. §102(b) is improper and the applicants respectfully request the withdrawal of this rejection.

New Claims 45-46

As the Examiner and the Applicants' representative discussed, the Examiner interprets the term "mutant" to be of a breadth sufficient to encompass the Fab2 of Stickney. In contrast, Applicants intend "mutant" to have its art-recognized meaning ("differing from the normal or wild type as a result of a change in the sequence of its DNA").

A ready solution to the incompatible definitions of "mutant" is the entry of new claims 45-46, further clarifying that "mutant" refers to a reactive group on the mutant antibody that is introduced by a mutation at the level of the nucleic acid that encodes the peptide.

The newly submitted claims further distinguish the present invention from Stickney, which is no longer an anticipatory reference against these claims. Accordingly, Applicants request entry of claims 45-46 and an indication of their allowability over the art of record.

Claims 2 and 3

The Examiner and Applicants' representative discussed the patentability of claims 2 and 3. Applicants representative is under the impression that the Examiner was substantially in agreement that Stickney does not anticipate claims 2 and 3 for the following reason. Assuming arguendo that Stickney teaches a Fab' with an amino acid residue functionalized with a linker bearing a reactive maleimide moiety, this linker does not fall within the scope of a side-chain of an amino acid. Accordingly, even if Stickney taught a species bearing a reactive linker arm, which it doesn't, this linker arm is not a side chain of an amino acid. Moreover, the

-Linker-thioether-Fab' species of Fab'-thioether-Linker-thioether-Fab' is not properly interpreted as a side chain of an amino acid. Thus, Stickney does not teach a reactive mutant in which the reactive site is the side chain of an amino acid.

Furthermore, claim 3 expressly recites that the side chain is the SH group of cysteine. As Applicants understand the Examiner's interpretation of Stickney, the reactive site is a free maleimide moiety of the linker arm, one terminus of which is bound to a cysteine residue; this feature does not correspond to the recited side chain of cysteine. Furthermore, as discussed above, the putative species comprising the reactive group does not exist in the scheme provided by Stickney. Thus, claims 2 and 3 are not anticipated by Stickney.

Under 35 U.S.C. §103(a)

Over Reardon et al., in view of Orlandi et al., Pastan et al., and Goodwin et al.

Claim 43 is rejected under 35 U.S.C. §103(a) as being allegedly obvious over the combination cited above. Without acceding to the Examiner's interpretation of the references or the patentability of the claim, solely to expedite prosecution, Applicants cancel claim 43. The applicants expressly reserve the right to pursue a claim of the same or similar scope as that of claim 43 in a continuation or divisional application.

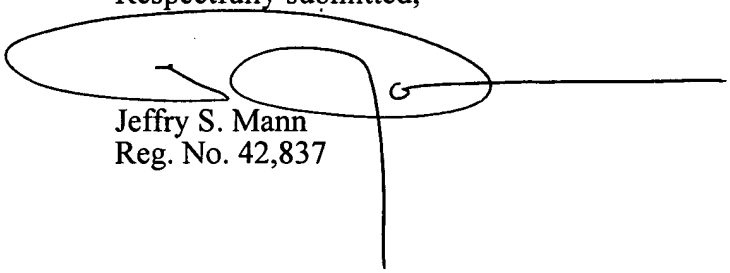
Since claim 43 is canceled, the rejection under 35 U.S.C. §103(a) is rendered moot. Hence, applicants respectfully request its withdrawal.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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